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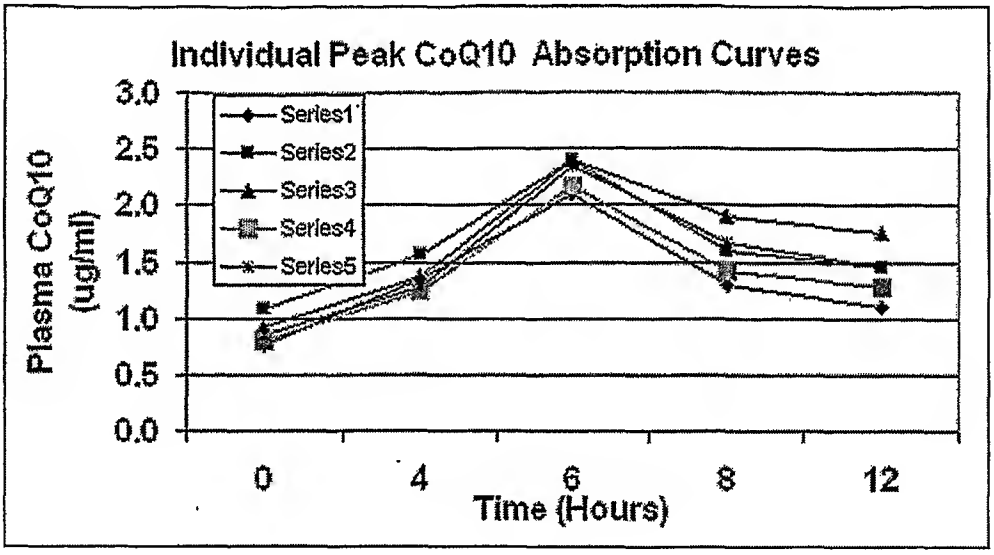
(54) Title: SOLUBILIZED CoQ-10



(57) Abstract: The present invention is directed to compositions and methods of delivery of CoQ-10 solubilized in monoterpenes. Use of monoterpenes as dissolving agents, greatly effects the ability to incorporate greater amounts of bioactive CoQ-10 in formulations, such as soft gel capsules.

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SOLUBILIZED CoQ-10

CROSS-REFERENCE TO RELATED APPLICATION

[001] This is a Continuation-in-Part application that claims benefit under 35 U.S.C. §120 to application Serial No. 10/674,268, filed September 29, 2003, entitled "Solubilized CoQ-10" (Attorney Docket No. 33503/US), the contents of which are incorporated herein in their entirety for all purposes.

FIELD OF THE INVENTION

[002] The present invention relates to the solubilization of coenzyme Q-10 and analogs thereof in monoterpenes, thereby providing increased bioavailability in delivery.

BACKGROUND OF THE INVENTION

[003] CoQ-10 (coenzyme Q10) is a fat-soluble quinone that is structurally similar to vitamin K and commonly known as ubiquinone. CoQ-10 is found in most living organisms, and is essential for the production of cellular energy. CoQ-10 (2,3 dimethyl-5 methyl-6-decaprenyl benzoquinone) is an endogenous antioxidant found in small amounts in meats and seafood. Although CoQ-10 is found in all human cells, the highest concentrations of CoQ-10 occur in the heart, liver, kidneys, and pancreas. It is found naturally in the organs of many mammalian species.

[004] CoQ-10 can be synthesized in the body or it can be derived from dietary sources. Situations may arise, however, when the need for CoQ-10 surpasses the body's ability to synthesize it. CoQ-10 can be absorbed by oral supplementation as evidenced by significant increases in serum CoQ-10 levels after supplementation.

[005] CoQ-10 is an important nutrient because it lies within the membrane of a cell organelle called the mitochondria. Mitochondria are known as the "power house" of the cell because of their ability to produce cellular energy, or ATP, by shuttling protons derived from nutrient breakdown through the process of aerobic (oxygen) metabolism. CoQ-10 also has a secondary role as an antioxidant. CoQ-10, due to the involvement in ATP synthesis, affects the

function of almost all cells in the body, making it essential for the health of all human tissues and organs. CoQ-10 particularly effects the cells that are the most metabolically active: heart, immune system, gingiva, and gastric mucosa

[006] Several clinical trials have shown CoQ-10 to be effective in supporting blood pressure and cholesterol levels. Furthermore, CoQ-10 has also been shown to improve cardiovascular health. CoQ-10 has been implicated as being an essential component in thwarting various diseases such as certain types of cancers. These facts lead many to believe that CoQ-10 supplementation is vital to an individual's well being.

[007] CoQ-10 is sparingly soluble in most hydrophilic solvents such as water. Therefore, CoQ-10 is often administered in a powdered form, as in a tablet or as a suspension. However, delivery of CoQ-10 by these methods limits the bioavailability of the material to the individual.

[008] There is a need in the art for an improved methodology to deliver increased amount of bioavailable CoQ-10 to an individual in need thereof.

BRIEF SUMMARY OF THE INVENTION

[009] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) and related analogs thereof can be readily dissolved in varying concentrations in monoterpenes. Generally, until the present discovery, most CoQ-10 liquid delivery methods could solubilize only up to about 5% by weight of the CoQ-10 in the "solvent". Typical solvents included various oils or the CoQ-10 was held in suspension. The present invention provides the ability to solubilize CoQ-10 in monoterpenes in concentrations of up to about 60% (weight to weight) without the need to aggressively heat the solution or with gentle warming. In particular, the solubilization of the CoQ-10 with monoterpenes can be accomplished at ambient temperatures.

[010] In one aspect, the present invention pertains to compositions that include coenzyme Q-10 or an analog thereof with a sufficient quantity of a monoterpene that is suitable to solubilize said coenzyme Q-10 and a pharmaceutically acceptable carrier. Generally, about 30 to about 45% of the

CoQ-10 (by weight) is solubilized in the monoterpene. In particular, the monoterpene is limonene. The compositions of the invention are useful as dietary supplements or as nutriceuticals.

[011] In particular, the compositions of the invention are included in a soft gelatin (soft gel) capsule. Typically, the soft gelatin capsule includes at least 5% by weight of coenzyme Q-10 or an analog thereof solubilized in a monoterpene. Typical monoterpenes include, for example, perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

[012] In another embodiment, the present invention pertains to methods for delivery of an effective amount of bioavailable CoQ-10 to an individual. The method includes providing CoQ-10 solubilized in a monoterpene, such that an effective amount of CoQ-10 is provided to the individual.

[013] In still another embodiment, the present invention also includes packaged formulations of the invention that include a monoterpene as a solvent for the CoQ-10 and instructions for use of the tablet, capsule, elixir, etc.

[014] In one aspect, the present invention provides solubilized coenzyme Q-10 compositions that include coenzyme Q-10 or an analog thereof, a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, and an acceptable carrier. The compositions provide a percentage of coenzyme Q-10 dosage that is absorbed by an individual of between about 5 percent and about 12 percent of said coenzyme Q-10 or analog thereof that is administered. The ranges of absorbed coenzyme Q-10 are from about 5 percent to about 12 percent, from about 6 percent to about 10 percent, and from about 6.5 percent to about 9.5 percent, based on the dosage of coenzyme Q-10 or analog thereof taken.

[015] In another aspect, the present invention provides solubilized coenzyme Q-10 compositions that include coenzyme Q-10 or an analog thereof, a

sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, and an acceptable carrier. The compositions provide a bioavailable steady state plasma level of coenzyme Q-10 or an analog thereof of between about 2.5 μg/ml to about 3.5 μg/ml. Suitable ranges of steady state plasma levels of coenzyme Q-10 or analog thereof are from about 2.5 μg/ml to about 3.5 μg/ml, from about 2.75 μg/ml to about 3.25 μg/ml and from about 2.75 μg/ml to about 3.0 μg/ml, based on the dosage of coenzyme Q-10 or analog thereof taken.

[016] In still yet another aspect, the present invention provides compositions that include solubilized coenzyme Q-10 or an analog thereof, a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, and an acceptable carrier. The compositions provide a peak plasma level of coenzyme Q-10 or analog thereof of between about 2.1 μg/ml to about 3.0 μg/ml. Suitable ranges of peak plasma levels of coenzyme Q-10 or analog thereof are from about 2.1 μg/ml to about 3.0 μg/ml, from about 2.2 μg/ml to about 2.8 μg/ml and from about 2.2 μg/ml to about 2.5 μg/ml.

[017] In another aspect, the present invention pertains to methods for delivery of an effective amount of bioavailable CoQ-10 to an individual. The methods include providing CoQ-10 solubilized in a monoterpene, such that an effective amount of CoQ-10 is provided to the individual so that the dosage absorbed, the steady state plasma levels of coenzyme Q-10, or the peak plasma levels of coenzyme Q-10 are sustained.

[018] In still another embodiment, the present invention also includes packaged formulations of the invention that include a monoterpene as a solvent for the CoQ-10 and instructions for use of the tablet, capsule, elixir, etc. so that the dosage absorbed, the steady state plasma levels of coenzyme Q-10, or the peak plasma levels of coenzyme Q-10 are sustained.

[019] While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the

art from the following detailed description, which shows and describes illustrative embodiments of the invention. As will be realized, the invention is capable of modifications in various obvious aspects, all without departing from the spirit and scope of the present invention. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not restrictive.

BRIEF DESCRIPTION OF THE FIGURES

[020] Figure 1 depicts individual single dose (60 mg) peak absorption curves for solubilized coenzyme Q-10;

[021] Figure 2 shows individual daily dose (60 mg/day) steady state plasma coenzyme Q-10 bioavailability curves for the solubilized coenzyme Q-10;

[022] Figure 3 provides a graphical representation of single dose peak absorption curves for the solubilized coenzyme Q-10 (60 mg) (upper line, ♦)(Example 5) formulation and Example 6 (30 mg) (lower line, ■). The Cmax for both formulations occurred at 6 hours. The change in plasma coenzyme Q-10 at Cmax was significantly greater for the solubilized coenzyme Q-10 by a three fold factor. The calculated percentage of dose absorbed at Cmax was 7.95 percent for the solubilized coenzyme Q-10 as compared to 6.04 percent for Example 6; and

[023] Figure 4 is a graphical representation of the steady state bioavailability curves for the solubilized coenzyme Q-10 (upper line, ♦)(Example 5) and Example 6 (lower line, ■) at a daily dose of 60 mg/day. Plasma levels at 7, 14, 21 and 28 days were significant ($P<0.01$) for the solubilized coenzyme Q-10 formulation.

DETAILED DESCRIPTION

[024] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) can be readily dissolved in varying concentrations in monoterpenes. CoQ-10 is found in most living organisms, and is essential for the production of cellular energy. Ubiquinone is a naturally occurring hydrogen carrier in the respiratory chain (coenzyme Q) and structurally, it is a 2,3-dimethoxy-5-methyl-1,4-benzoquinone with a multiprenyl side chain, the number of isoprene units varying depending upon the organism from which it is derived. CoQ-10 analogs include reduced and semi-reduced CoQ-10 and ubiquinone derivatives described, for example, in WO 8803015, the teachings of which are incorporated herein by reference.

[025] Generally, until the present discovery, most CoQ-10 liquid delivery methods could solubilize only up at most about 10% by weight of the CoQ-10 in the solvent. Typical solvents included oils or the CoQ-10 was held in an aqueous suspension. Alternatively, the CoQ-10 was provided as a solid in a tablet or powder.

[026] The present invention provides the ability to solubilize CoQ-10 and analogs thereof in monoterpenes, as defined herein, in concentrations of up to about 60% (weight to weight) without the need to heat the solution. In one aspect, the monoterpene solubilizes CoQ-10 from about 0.1 percent by weight to about 45 percent by weight.

[027] In particular, the solubilization of the CoQ-10 and analogs thereof with monoterpenes can be accomplished at ambient temperatures. In one aspect, from about 5 to about 50 percent (weight CoQ-10/weight solvent) CoQ-10 can be solubilized in a monoterpene. In another aspect, from about 15 to about 40 percent w/w can be solubilized and in still another aspect, from about 20 to about 35 percent w/w CoQ-10 can be solubilized in a monoterpene.

[028] The phrase "sufficient quantity of a monoterpene suitable to solubilize coenzyme Q-10" is therefore intended to mean that that amount of a

monoterpene that will dissolve CoQ-10 under a given set of conditions, generally, those at ambient temperature. This determination should be understood by one skilled in the art and can be determined by methods known in the art, such as by solubility studies.

[029] One of the particular advantages of utilizing monoterpenes in combination with CoQ-10 and analogs thereof is that the enzyme is dissolved by the monoterpene. That is, many formulations currently in the marketplace have CoQ-10 present as a suspension; a situation where not all the CoQ-10 is dissolved. This reduces efficacy and the bioavailability of the CoQ-10. The present invention eliminates this disadvantage by solubilizing the CoQ-10 in the monoterpene.

[030] A particular advantage in using monoterpenes is that the CoQ-10 or analog thereof does not have to be heated to dissolve into solution. This is important so that the CoQ-10 or analog thereof does not degrade upon dissolution.

[031] The term "monoterpene" as used herein, refers to a compound having a 10-carbon skeleton with non-linear branches. A monoterpene refers to a compound with two isoprene units connected in a head-to-end manner. The term "monoterpene" is also intended to include "monoterpenoid", which refers to a monoterpene-like substance and may be used loosely herein to refer collectively to monoterpenoid derivatives as well as monoterpenoid analogs. Monoterpenoids can therefore include monoterpenes, alcohols, ketones, aldehydes, ethers, acids, hydrocarbons without an oxygen functional group, and so forth.

[032] It is common practice to refer to certain phenolic compounds, such as eugenol, thymol and carvacrol, as monoterpenoids because their function is essentially the same as a monoterpenoid. However, these compounds are not technically "monoterpenoids" (or "monoterpenes") because they are not synthesized by the same isoprene biosynthesis pathway, but rather by production of phenols from tyrosine. However, common practice will be followed herein. Suitable examples of monoterpenes include, but are not limited to, limonene,

pinene, cintronellol, terpinene, nerol, menthane, carveol, S-linalool, safrol, cinnamic acid, apiol, geraniol, thymol, citral, carvone, camphor, etc. and derivatives thereof. For information about the structure and synthesis of terpenes, including terpenes of the invention, see Kirk-Othmer Encyclopedia of Chemical Technology, Mark, et al., eds., 22:709-762 3d Ed (1983), the teachings of which are incorporated herein in their entirety.

[033] In particular, suitable limonene derivatives include perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

[034] Formulation of the CoQ-10 and analogs thereof can be accomplished by many methods known in the art. For example, the solubilized CoQ-10 or analog thereof can be formulated in a suspension, an emulsion, an elixir, a solution, a caplet that harbors the liquid, or in a soft gelatin capsule. Often the formulation will include an acceptable carrier, such as an oil, or other suspending agent.

[035] Suitable carriers include but are not limited to, for example, fatty acids, esters and salts thereof, that can be derived from any source, including, without limitation, natural or synthetic oils, fats, waxes or combinations thereof. Moreover, the fatty acids can be derived, without limitation, from non-hydrogenated oils, partially hydrogenated oils, fully hydrogenated oils or combinations thereof. Non-limiting exemplary sources of fatty acids (their esters and salts) include seed oil, fish or marine oil, canola oil, vegetable oil, safflower oil, sunflower oil, nasturtium seed oil, mustard seed oil, olive oil, sesame oil, soybean oil, corn oil, peanut oil, cottonseed oil, rice bran oil, babassu nut oil, palm oil, low erucic rapeseed oil, palm kernel oil, lupin oil, coconut oil, flaxseed oil, evening primrose oil, jojoba, tallow, beef tallow, butter, chicken fat, lard, dairy butterfat, shea butter or combinations thereof.

[036] Specific non-limiting exemplary fish or marine oil sources include shellfish oil, tuna oil, mackerel oil, salmon oil, menhaden, anchovy, herring, trout, sardines or combinations thereof. In particular, the source of the fatty acids is fish or marine oil (DHA or EPA), soybean oil or flaxseed oil. Alternatively or in combination with one of the above identified carrier, beeswax can be used as a suitable carrier, as well as suspending agents such as silica (silicon dioxide).

[037] The formulations of the invention are considered dietary supplements useful to the increase the amounts of CoQ-10 and analogs thereof in the individuals in need thereof.

[038] Alternatively, the formulations of the invention are also considered to be nutraceuticals. The term "nutraceutical" is recognized in the art and is intended to describe specific chemical compounds found in foods that may prevent disease. CoQ-10 or an analog thereof are such compounds.

[039] The formulations of the invention can further include various ingredients to help stabilize, or help promote the bioavailability of the CoQ-10 and analogs thereof, or serve as additional nutrients to an individual's diet. Suitable additives can include vitamins and biologically-acceptable minerals. Non-limiting examples of vitamins include vitamin A, B vitamins, vitamin C, vitamin D, vitamin E, vitamin K and folic acid. Non-limiting examples of minerals include iron, calcium, magnesium, potassium, copper, chromium, zinc, molybdenum, iodine, boron, selenium, manganese, derivatives thereof or combinations thereof. These vitamins and minerals may be from any source or combination of sources, without limitation. Non-limiting exemplary B vitamins include, without limitation, thiamine, niacinamide, pyridoxine, riboflavin, cyanocobalamin, biotin, pantothenic acid or combinations thereof.

[040] Vitamin(s), if present, are present in the composition of the invention in an amount ranging from about 5 mg to about 500 mg. More particularly, the vitamin(s) is present in an amount ranging from about 10 mg to about 400 mg. Even more specifically, the vitamin(s) is present from about 250

mg to about 400 mg. Most specifically, the vitamin(s) is present in an amount ranging from about 10 mg to about 50 mg. For example, B vitamins are in usually incorporated in the range of about 1 milligram to about 10 milligrams, i.e., from about 3 micrograms to about 50 micrograms of B12. Folic acid, for example, is generally incorporated in a range of about 50 to about 400 micrograms, biotin is generally incorporated in a range of about 25 to about 700 micrograms and cyanocobalamin is incorporated in a range of about 3 micrograms to about 50 micrograms.

[041] Mineral(s), if present, are present in the composition of the invention in an amount ranging from about 25 mg to about 1000 mg. More particularly, the mineral(s) are present in the composition ranging from about 25 mg to about 500 mg. Even more particularly, the mineral(s) are present in the composition in an amount ranging from about 100 mg to about 600 mg.

[042] Various additives can be incorporated into the present compositions. Optional additives of the present composition include, without limitation, phospholipids, L-carnitine, starches, sugars, fats, antioxidants, amino acids, proteins, flavorings, coloring agents, hydrolyzed starch(es) and derivatives thereof or combinations thereof.

[043] As used herein, the term "phospholipid" is recognized in the art, and refers to phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl serine, phosphatidyl choline, phosphatidyl ethanolamine, as well as phosphatidic acids, ceramides, cerebrosides, sphingomyelins and cardiolipins.

[044] L-carnitine is recognized in the art and facilitates transport of materials through the mitochondrial membrane. L-carnitine is an essential fatty acid metabolism cofactor that helps to move fatty acids to the mitochondria from the cytoplasm. This is an important factor as this is where CoQ-10 uptake occurs.

[045] In one aspect of the present invention, L-carnitine is included in soft gel formulations in combination with CoQ-10 or an analog thereof. Suitable ratios of L-carnitine and CoQ-10 are known in the art and include those described

in US Patent No. 4,599,232, issued to Sigma Tau Industrie Faramaceutiche Riunite S.p.A. on July 8, 1986, the teachings of which are incorporated herein in their entirety. In particular, combinations of limonene, CoQ-10 and L-carnitine in soft gel formulations are of importance. The present invention provides the advantage of solvating large amounts (relative to that of current state of the art) of CoQ-10 in limonene in a soft gel capsule along with an additive, such as L-carnitine.

[046] As used herein, the term "antioxidant" is recognized in the art and refers to synthetic or natural substances that prevent or delay the oxidative deterioration of a compound. Exemplary antioxidants include tocopherols, flavonoids, catechins, superoxide dismutase, lecithin, gamma oryzanol; vitamins, such as vitamins A, C (ascorbic acid) and E and beta-carotene; natural components such as camosol, carnosic acid and rosmanol found in rosemary and hawthorn extract, proanthocyanidins such as those found in grapeseed or pine bark extract, and green tea extract.

[047] The term "flavonoid" as used herein is recognized in the art and is intended to include those plant pigments found in many foods that are thought to help protect the body from cancer. These include, for example, epi-gallo catechin gallate (EGCG), epi-gallo catechin (EGC) and epi-catechin (EC).

[048] The phrase "solubilized CoQ-10 and analogs thereof" is intended to mean that the coenzyme Q-10 is solvated by the lipophilic materials incorporated into the soft gel capsule. Typical capsules that contain CoQ-10 or an analog thereof include the coenzyme or analog as a dry powder or as a suspension of crystals. It is believed that the powder or crystallinity of the coenzyme does not facilitate absorption by the cells. The present invention overcomes this disadvantage by providing formulations wherein the coenzyme is not in a powdered or crystalline form. Microscopic evaluations of the lipophilic formulations do not show crystals of the coenzyme. Consequently, it is believed that the solvated coenzyme can more easily pass into cells. This is highly

advantageous in delivering increased amounts of the coenzyme into an individual's physiological make up.

[049] Any dosage form, and combinations thereof, are contemplated by the present invention. Examples of such dosage forms include, without limitation, chewable tablets, elixirs, liquids, solutions, suspensions, emulsions, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, suppositories, creams, topicals, ingestibles, injectables, infusions, health bars, confections, animal feeds, cereals, cereal coatings, and combinations thereof. The preparation of the above dosage forms are well known to persons of ordinary skill in the art.

[050] For example, health bars can be prepared, without limitation, by mixing the formulation plus excipients (e.g., binders, fillers, flavors, colors, etc.) to a plastic mass consistency. The mass is then either extended or molded to form "candy bar" shapes that are then dried or allowed to solidify to form the final product.

[051] Soft gel or soft gelatin capsules can be prepared, for example, without limitation, by dispersing the formulation in an appropriate vehicle (e.g. rice bran oil, monoterpene and/or beeswax) to form a high viscosity mixture. This mixture is then encapsulated with a gelatin based film using technology and machinery known to those in the soft gel industry. The industrial units so formed are then dried to constant weight. Typically, the weight of the capsule is between about 100 to about 2500 milligrams and in particular weigh between about 1500 and about 1900 milligrams, and more specifically can weigh between about 1500 and about 2000 milligrams.

[052] For example, when preparing soft gelatin shells, the shell can include between about 20 to 70 percent gelatin, generally a plasticizer and about 5 to about 60% by weight sorbitol. The filling of the soft gelatin capsule is liquid (principally limonene, in combination with rice bran oil and/or beeswax if desired) and can include, apart form the antioxidant actives, a hydrophilic matrix.

The hydrophilic matrix, if present, is a polyethylene glycol having an average molecular weight of from about 200 to 1000. Further ingredients are optionally thickening agents. In one embodiment, the hydrophilic matrix includes polyethylene glycol having an average molecular weight of from about 200 to 1000, 5 to 15% glycerol, and 5 to 15% by weight of water. The polyethylene glycol can also be mixed with propylene glycol and/or propylene carbonate.

[053] In another embodiment, the soft gel capsule is prepared from gelatin, glycerine, water and various additives. Typically, the percentage (by weight) of the gelatin is between about 30 and about 50 weight percent, in particular between about 35 and about weight percent and more specifically about 42 weight percent. The formulation includes between about 15 and about 25 weight percent glycerine, more particularly between about 17 and about 23 weight percent and more specifically about 20 weight percent glycerine.

[054] The remaining portion of the capsule is typically water. The amount varies from between about 25 weigh percent and about 40 weight percent, more particularly between about 30 and about 35 weight percent, and more specifically about 35 weight percent. The remainder of the capsule can vary, generally, between about 2 and about 10 weight percent composed of a flavoring agent(s), sugar, coloring agent(s), etc. or combination thereof. After the capsule is processed, the water content of the final capsule is often between about 5 and about 10 weight percent, more particularly 7 and about 12 weight percent, and more specifically between about 9 and about 10 weight percent.

[055] As for the manufacturing, it is contemplated that standard soft shell gelatin capsule manufacturing techniques can be used to prepare the soft-shell product. Examples of useful manufacturing techniques are the plate process, the rotary die process pioneered by R. P. Scherer, the process using the Norton capsule machine, and the Accogel machine and process developed by Lederle. Each of these processes are mature technologies and are all widely available to any one wishing to prepare soft gelatin capsules.

[056] Typically, when a soft gel capsule is prepared, the total weight is between about 250 milligrams and about 2.5 gram in weight, e.g., 400-750 milligrams. Therefore, the total weight of additives, such as vitamins and antioxidants, is between about 80 milligrams and about 2000 milligrams, alternatively, between about 100 milligrams and about 1500 milligrams, and in particular between about 120 milligrams and about 1200 milligrams.

[057] For example, a soft gel capsule can be prepared by mixing a 35% solution of CoQ-10 and limonene (w/w) (e.g., 104 milligrams of CoQ-10 in 193.14 milligrams of limonene) with between about 0.01 grams and about 0.4 grams (e.g., 0.1 grams) tocopherol, between about 200 grams and about 250 grams (e.g., 225 grams) rice bran oil and between about 0.01 grams and about 0.5 grams betacarotene (e.g. about 0.02 grams). The mixture is then combined with encapsulated within a gelatin capsule as described above.

[058] The present invention also provides packaged formulations of a monoterpene with CoQ-10 and instructions for use of the tablet, capsule, elixir, etc. Typically, the packaged formulation, in whatever form, is administered to an individual in need thereof that requires and increase in the amount of CoQ-10 in the individual's diet. Typically, the dosage requirements is between about 1 to about 4 dosages a day.

[059] CoQ-10 has been implicated in various biochemical pathways and is suitable for the treatment of cardiovascular conditions, such as those associated with, for example, statin drugs that effect the body's ability to produce CoQ-10 naturally. CoQ-10 has also been implicated in various periodontal diseases. Furthermore, CoQ-10 has been implicated in mitochondrial related diseases and disorders, such as the inability to product acetyl coenzyme A, neurological disorders, for example, such as Parkinson's disease and, Prater-Willey syndrome.

[060] The following examples are intended to be illustrative only and should not be considered limiting.

[061] **Examples**

[062] Formulations of CoQ-10 can be prepared in the following ratios by mixing the components together and then placing into a soft gel capsule.

Component	Example 1	Example 2
CoQ-10	104.09 mg	104.09 mg
Mixed Tocopherols (372 IU/g)	269.03 mg	269.03 mg
Rice Bran Oil	176.02 mg	----------
Natural Beta Carotene (20% by weight)	10.05 mg	10.05 mg
Yellow Beeswax	20.0 mg	----------
D-limonene	----------	196.02 mg
Total weight	580 mg	580 mg

[063] Example 2 demonstrates that the use of limonene solubilizes CoQ-10 without the requirement of beeswax and/or rice bran oil being present. Examples 1 and 2 can be incorporated into soft gel capsules by standard methods known in the art.

Component	Example 3	Example 4
CoQ-10	17.95 g	17.95 g
EPAX 2050TG	48.77 g	45.49 g
D-Limonene	35.70 g	35.70 g
5-67 Tocopherol (1000 IU/g)	-------	0.86 g

[064] Examples 3 and 4 demonstrate that CoQ-10 can be solubilized in scalable quantities. Additives, such as EPAX 2050 TG (an ω-3 oil; 20% EPA/50% DHA as triglycerides, remainder fatty acid/triglycerides; Pronova Biocare) and tocopherols (5-67 Tocopherol; BD Industries) can easily be incorporated into such limonene containing formulations. The resultant mixtures contained approximately 100 mg of CoQ-10 per soft gel capsule. Preparation of the soft gel capsules was accomplished by methods well known in the art.

Component	Example 5	Example 6
CoQ-10 (98%)	62.45 mg	62.45 mg
Vitamin E mixed tocopherols (700 mg/g)	69.19 mg	161.3. mg
D-Limonene	118.1 mg	none
Soybean oil	30.26 mg	none
5-67 Tocopherol (1000 IU/g)	60.0 mg	none
yellow beeswax	none	15.0 mg
Rice bran oil	none	188.71 mg
Natural beta Carotene	none	7.54 mg
	mg/capsule	mg/capsule

[065] Examples 5 and 6 provide a comparison between soft gel capsules prepared with D-limonene and without D-limonene and enzyme CoQ-10. Examples 5 and 6 will be referred to throughout the following paragraphs to show efficacy in delivery with the use of the monoterpene, D-limonene.

[066] The single 60 mg dose peak absorption characteristics and the 28-day 60 mg daily dose steady state bioavailability of the solubilized CoQ_{10} formulation was determined in five (5) normal male (N=3) and female (N=2)

volunteers. The peak absorption study was done over 12 hours. For the control sample, the volunteers were in a rested and fasted condition-minimum eight (8) hours. Serial blood samples were taken at 0, 4, 6, 8, and 12 hours after ingesting 60 mg of a softgel product (either solubilized CoQ_{10} (Example 5) or Example 6, a non-solubilized CoQ_{10} formulation. In the steady state bioavailability study, daily doses of 60 mg of the solubilized CoQ_{10} formulation were taken with breakfast. CoQ_{10} in plasma was measured using the hexane extraction and HPLC detection method described in "A New Method to Determine the Level of Coenzyme Q10 in One Drop of Human Blood for Biomedical Research", Manabu Morita and Karl Folkers, Biochem. Biophys. Res. Commun. 191(3), 950-954,1993, the contents of which are incorporated herein in their entirety. The solubilized CoQ_{10} formulation was a soft gel capsule that contained 60 mg CoQ_{10}, 118.1 mg limonene, 30.26 mg soybean oil and vitamin E as described in Example 5. The non-solubilized formulation was a soft gel capsule that contained 60 mg CoQ_{10}, 188.71 mg rice bran oil, 161.3 mg vitamin E (and additional additives) as described in Example 6.

[067] Group mean control plasma CoQ_{10} level (0.88±0.13 μg/ml) was in the normal range. Tmax after ingestion of a single 60 mg capsule was in six (6) hours and the mean peak plasma level (Cmax) was 2.28±0.14μg/ml. The amount of solubilized CoQ_{10} absorbed at Cmax was 4,765.51±825.39μg or 7.96±1.38 % of the ingested dose. With daily dosing the plasma solubilized CoQ_{10} level increased to a mean plateau level of 2.68±0.15μg/ml in 14 days and remained fairly constant thereafter. The 28-day plasma level was 2.75±0.22μg/ml. The solubilized CoQ_{10} bioavailability in plasma was 6,498.90±1,634.76μg, and the area under the plasma time base curve was 42.27±2.29μg/ ml• day. These data demonstrate that the solubilized CoQ_{10} formulation was absorbed significantly ($p<0.001$). The peak absorption of 7.96% of the ingested dose and the steady state bioavailability after 28 days was significantly ($p<0.01$) greater than that found in Example 6.

[068] The solubilized CoQ_{10} formulation (Example 5) absorption is greater than that of most softgel CoQ_{10} products in which CoQ_{10} crystals are suspended in a lipid base and those products that provide only a dried powder composition.

Peak Absorption Characteristics and Steady State Bioavailability of Solubilized CoQ_{10} formulation

[069] The use of Coenzyme Q_{10} (CoQ_{10}) around the world has surpassed the production capabilities of the Japanese producers. CoQ_{10} is also rapidly entering the clinical consumer market with the positive study reports on heart failure, Parkinson's disease, muscular ataxias, low energy genetic syndromes, statin drug inhibition of CoQ_{10} synthesis and recent publications that show that CoQ_{10} and its precursors in the body inhibit farensyl-transferase and thus turn off the growth and rapid division of cancer cells. With these advances in CoQ_{10} research and the conclusions that plasma CoQ_{10} levels for clinical efficacy should be raised to about 3.2 μg/ml, more companies have been seeking to develop CoQ_{10} products with improved absorption and steady state bioavailability. The absorption of CoQ_{10} is not the same for all CoQ_{10} products found in the market place. In general dry powder delivery systems have 0.5 to 2% peak absorption. Dry powder CoQ_{10} in a lipid base that is incorporated into soft gelatin capsules has better peak absorption (2.0-3.0%). This appears to be dependant on the number and size of the CoQ_{10} crystals in the product.

[070] The following data relate to peak absorption characteristics of a single 60 mg dose and the steady state bioavailability of a daily 60mg dose for the solubilized CoQ_{10} softgel formulation. Both studies were conducted on the same five (5) normal volunteer subjects. Peak absorption and steady state bioavailability characteristics were compared to that of Example 6 which was collected using a similar study design but different volunteers.

Methods

[071] Five normal volunteers (3 males/2 females) were randomly selected from a screened group of 15 individuals (Table I). The exclusion criteria were: 1) smoker, 2) individual taking a CoQ_{10} product, 3) individual with high plasma cholesterol, 4) individual taking drugs known to interfere with endogenous synthesis or CoQ_{10} absorption, 5) individual on vegetarian diet, and 6) athlete.

Table I: Physical Characteristics of Study Volunteers

VOLUNTEER	AGE YEARS	SEX	HEIGHT INCHES	WEIGHT POUNDS	PLASMA VOLUME MILLILITERS
PDOB 01	43	F	63.50	147.00	3139.00
RFRE 02	42	M	66.25	170.75	3720.00
AJOH 03	43	M	69.50	205.00	3928.00
SHAL 04	26	M	70.50	192.50	3870.00
NJOH 05	39	F	63.75	126.00	2520.00

[072] After being fully familiarized with the experimental design and their responsibilities, the volunteers had their questions answered by the principle investigator, and read and signed a volunteer consent form. On day 0 of the study, volunteers reported to the testing facility at 0600 in a rested and fasted state-minimum eight (8) hours. Vital signs were taken, an intercath was placed in a forearm vein, and a control blood sample was collected for determining the control CoQ_{10} plasma level. The volunteers were then given a single 60 mg dose of the solubilized CoQ_{10} formulation. This was followed by a breakfast consisting of orange juice or milk (2%) with a bagel or cereal. Blood samples were drawn again at hours 4, 6, 8 and 12; vital signs and safety data were collected simultaneously. Starting with day 1 of the study, the volunteers took 60 mg of solubilized CoQ_{10} formulation daily for the next 28 days. During this time, volunteers followed their regular diet and activity schedules and returned to the testing facility on days 7, 14, 21, and 28 at 0600 in a rested and fasted condition-minimum eight (8) hours-for the purpose of collecting vital signs and safety data,

and to have a venous blood sample collected from which plasma CoQ_{10} levels were determined.

[073] All CoQ_{10} samples were collected in vaccutainers containing EDTA to prevent clotting. The samples were cooled in ice water and then centrifuged to separate the plasma from the formed elements. The plasma was pipetted into a sealable transfer container, labeled according to volunteer identification and hour of collection and frozen at -20° centigrade. All plasma samples were shipped overnight in dry ice to an independent laboratory for CoQ_{10} analysis. The method used was that as described in Morita & Folkers (*supra*) hexane extraction and HPLC detection.

[074] Individual volunteer data points were entered into a Microsoft Excel spreadsheet. Descriptive statistics were used to calculate group means SD and SE. Statistical differences between group control and each group sample for the peak absorption and the steady state weekly levels were determined using a standard t-test for differences between group means. A probability of $p \leq 0.05$ was accepted as significant.

Results

I: Peak Absorption Study

[075] Individual and group means ± SE & SD descriptive statistics data for the 60 mg single dose peak absorption study are presented in Table II and the individual data plotted on a 12 hour time base are shown in Figure 1. Control plasma CoQ_{10} was variable between volunteers (range = 0.77 -1.09µg/ml). The group means ± SD was 0.88±0.13µg/ml. This is considered to be in the normal range. Within four hours after ingesting the solubilized CoQ_{10} the plasma levels for the group increased significantly ($p \leq 0.01$) to 1.36±0.12µg/ml. Peak plasma levels occurred at six (6) hours (Tmax) and the maximum plasma concentration (Cmax) was 2.28±0.14µg/ml. Thereafter plasma CoQ_{10} rapidly decreased over

the next two hours to a mean level of 1.58±0.23μg/ml during the rapid tissue uptake period of CoQ_{10}. The peak absorption kinetics calculated from the peak absorption data are presented in Table IV.

Table II: Individual and Group Solubilized CoQ_{10} formulation : Single Dose (60mg) Peak Absorption Study

	Sample Time (Hours)				
	0	4	6	8	12
Volunteer					
1	0.77	1.35	2.09	1.30	1.10
2	1.09	1.56	2.40	1.60	1.46
3	0.92	1.36	2.39	1.90	1.76
4	0.79	1.24	2.16	1.42	1.27
5	0.85	1.28	2.34	1.67	1.45
Mean	0.88	1.36	2.28	1.58	1.41
Standard Error	0.06	0.06	0.06	0.10	0.11
Standard Deviation	0.13	0.12	0.14	0.23	0.25
P-value		3.24E-05	1.57E-06	0.000766	0.002338

[076] The amount of CoQ_{10} absorbed at Cmax was 4,769.51±825.39µg. When compared to the ingested dose (60,000 µg), the percent of the dose absorbed at Cmax was 7.95±1.38%. In the first two hours after Cmax an average of 2196.14±523.83µg was distributed out of the blood and into the body cells. The amount was 46.46±9.85 % of that absorbed at Cmax.

II: Steady State Plasma CoQ_{10} Bioavailability

[077] Individual and group means ± SD descriptive statistics data for the 28-day 60mg/ day steady state plasma CoQ_{10} bioavailability for the solubilized CoQ_{10} formulation are presented in Table III and graphically in Figures 2 and 4. Again there was a variation between volunteers. In seven (7) days the basal plasma CoQ_{10} level increased significantly ($p \leq 0.01$) to 2.39±0.13μg/ml. Plasma levels plateaued for each volunteer between the 7th and 14th day and remained fairly constant thereafter (Figure 2). At the 28th day the group means plasma CoQ_{10} level was 2.75±0.22μg/ml ($p \leq 0.001$). The calculated steady state increase in plasma CoQ_{10} was 6,458.90±1,634.76μg at a constant daily dose of 60mg/day (Table V). In a steady state condition the group mean relative increase in plasma CoQ_{10} was 314.42± 39.07%. The area under the plasma CoQ_{10} and time base curve between days 0 and 28 days ($AUC_{0\text{-}28day}$)(AUC denotes area under the curve) is used to equate the CoQ_{10} bioavailability. The AUC for this product was 42.27±2.29 μg/ ml•day.

Table III: Individual and Group Solubilized CoQ_{10}: Steady State (60mg/day) Plasma CoQ10 Bioavailability Study

	Time (Days)						
	0	7	14	21	28	% Change	AUC (0-28 day) ug/ml.day
Volunteer							
1	0.77	2.20	2.48	2.56	2.67	285.71	42.77
2	1.09	2.30	2.79	2.80	2.78	211.01	38.68
3	0.92	2.52	2.78	3.00	3.10	273.91	42.22
4	0.79	2.42	2.78	2.70	2.68	306.33	42.61
5	0.85	2.49	2.56	2.60	2.50	292.94	45.05
Mean	0.88	2.39	2.68	2.73	2.75	314.42	42.27
Standard Error	0.06	0.06	0.07	0.08	0.10	17.47	1.02
Standard Deviation	0.13	0.13	0.15	0.18	0.22	39.07	2.29
p-value		2.65E-05	3.11E-06	5.13E-06	5.13E-06		

Table IV: Individual and Group Single Dose Peak Absorption Characteristics for Solubilized CoQ_{10} formulation

	Control Plasma Q10 ug/ml	Plasma Cmax ug/ml	Change Plasma Q10 ug/ml	Plasma Vol ml	Change in Plasma Q10 ug	% of Dose Absorbed	Rapid Q10 Distribution ug/ml	Amt. Q10 Distributed ug	% Distributed of Amt. Absorbed
Volunteer									
1	0.77	2.09	1.32	3139.00	4143.48	6.91	0.61	1914.79	46.21
2	1.09	2.40	1.31	3720.00	4873.20	8.12	0.80	2976.00	61.07
3	0.92	2.39	1.47	3928.00	5774.16	9.62	0.49	1924.72	33.33
4	0.79	2.16	1.37	3870.00	5301.90	8.84	0.64	2476.80	46.72
5	0.85	2.34	1.49	2520.00	3754.80	6.26	0.67	1688.40	44.97
Mean	0.88	2.28	1.48	3435.40	4769.51	7.95	0.64	2196.14	46.46
SD	0.06	0.06	0.08	268.17	369.12	0.62	0.05	234.26	4.41
SE	0.13	0.14	1.39	599.65	825.39	1.38	0.11	523.83	9.85

III: Particle and Crystalline Characteristics of Solubilized CoQ_{10}

[078] Photomicrographs of solubilized CoQ_{10} (Example 5) and Example 6 showed that Example 6 had many small crystals of CoQ_{10}, whereas the solubilized CoQ_{10} (Example 5) showed no crystals, and appeared to be a homogenous distribution of CoQ_{10} molecules in solution.

Discussion

[079] The study determined the peak single dose (60mg) absorption characteristics and the steady state plasma CoQ_{10} bioavailability in response to a constant daily dose of 60mg/day for 28 days of solubilized CoQ_{10}. The control plasma CoQ_{10} data for the small group (N=5) was in the normal range (Tables 1 &2). The plasma CoQ_{10} increase at Cmax (2.28±0.14 μg/ml) was significantly ($p<0.001$) above the control level as was the amount of CoQ_{10} added to the plasma at Cmax (Table IV and V).

Table V: Individual and Group Solubilized CoQ_{10} (Example 5): Steady State (60mg/day) CoQ_{10} Bioavailability Study

	C-CoQ10 ug/ml	28 Day ug/ml	Change ug/ml	Plasma Vol ml	Plasma Q Change ug/ml	% Change	AUC (0-28 day) ug/ml.day
Volunteer							
1	0.77	2.67	1.90	3,139.00	5,964.10	346.75	42.77
2	1.09	2.78	1.69	3,720.00	6,286.80	255.05	38.68
3	0.92	3.10	2.18	3,928.00	8,563.04	336.96	42.22
4	0.79	2.68	1.89	3,870.00	7,314.30	339.24	42.61
5	0.85	2.50	1.65	2,525.00	4,166.25	294.12	45.05
Mean	0.88	2.75	1.86	3,436.40	6,458.90	314.42	42.27
Standard Error	0.06	0.10	0.09	267.32	731.09	17.47	1.02
Standard Deviation	0.13	0.22	0.21	597.75	1,634.76	39.07	2.29

[080] Peak absorption and steady state bioavailability data were compared between the solubilized CoQ_{10} (Example 5) and Example 6. Comparisons were made by examining Figures 3 and 4. These Figures show the peak absorption curves (Figure 3) and the steady state bioavailability curves (Figure 4) characteristics of both the solubilized CoQ_{10} and CoQ_{10sol} products plotted on the same time base. Cmax for Example 6 with a 30 mg dose increased 0.53±0.28 µg/ml above the control level. With this change in plasma CoQ_{10} 1813.33±96.65µg of CoQ_{10} was added to the blood at Cmax. The calculated percent (%) of ingested dose absorbed was 6.04±0.32 %. This is significantly less than the 1.48±0.39ug/ml change in plasma CoQ_{10} and the 7.95±1.38% of the 60 mg ingested dose of the solubilized CoQ_{10} formulation. Thus, the relative increases in the peak plasma CoQ_{10} at Cmax, the amount of CoQ_{10} absorbed at Cmax and the percent of ingested dose absorbed at Cmax between the solubilized CoQ_{10} (Example 5) and Example 6 formulations were 80, 60 and 40 percent greater respectively for the solubilized CoQ_{10} formulation. These data show that Example 6 at a dose of 30 mg is significantly ($p < 0.01$) less absorbed than 60 mg of solubilized CoQ_{10} formulation. The steady state bioavailability of Example 6 is also significantly less than that of solubilized CoQ_{10} formulation as shown in Figure 4.

[081] At 28 days with a 60 mg daily dose, Example 6 resulted in a group mean steady state plasma CoQ_{10} level of 2.26±0.74µg/ml. This is significantly ($p \leq 0.01$) less than the 2.75±0.22µg/ml measured for the solubilized CoQ_{10} formulation using the same 60 mg/day dose. Similarly, the AUCo-28 day for the solubilized CoQ_{10}, CoQ_{10} was significantly greater ($p \leq 0.01$) than that found for Example 6 (42.27±2.29 - vs. - 29.6±4.61µg/ml/day). These data comparisons also show that the solubilized CoQ_{10} formulation CoQ_{10} bioavailability is significantly greater than that of Example 6.

[082] Not to be limited by theory, as to why the solubilized CoQ_{10} formulation (Example 5) has better absorption than Example 6 may be explained

by the physical characteristics of the two formulations. Both Example 6 and the solubilized CoQ_{10} formulations were made by the same soft gel encapsulating process. The ingredients in the two formulations were different relative to the lipid carrier molecules (Rice bran oil in Example 6 and Soybean oil and D-Limonene oil in the solubilized CoQ_{10} formulation (Example 5)). On examination of the two formulations, the contents of both were an oily matrix. The solubilized CoQ_{10} formulation appeared to be more liquid (less solids) than Example 6. Example 6 was reddish brown in color due to the beta-carotene. The solubilized CoQ_{10} formulation was dark brown in color. Upon microscopic examination Example 6 was found to have small crystals, whereas the solubilized CoQ_{10} was devoid of crystals. It is postulated that the solubilized CoQ_{10} formulation consists of a larger fraction of single CoQ_{10} molecules and exerts a greater osmotic concentration of CoQ_{10} outside the intestinal cells, thus a greater driving force for the facilitated diffusion process for CoQ_{10} absorption.

[083] Since the CoQ_{10} crystal has a melting point 10° centigrade above body temperature (37°C) and completely melt to single molecules at 65° centigrade, it is believed that the lower absorption of Example 6 is due to the larger proportion of CoQ_{10} crystals in solution and the physiological fact that the body cannot absorb a crystal. Only single molecules in water or lipid solution can be absorbed across the intestinal mucosal membrane or transported across any epithelial cell membrane.

[084] In summary, the solubilized CoQ_{10} formulation peak absorption kinetics and steady state bioavailability is significantly greater than that of Example 6. The 7.95% absorption of the ingested dose makes this a superior composition to provide increased amounts of CoQ_{10} to a subject in need thereof.

[085] Although the present invention has been described with reference to preferred embodiments, persons skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

[086] All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.

Claims

What is claimed is:

1. A solubilized coenzyme Q-10 composition comprising:

coenzyme Q-10 or an analog thereof;

a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof; and

an acceptable carrier, wherein said composition provides an absorbed percentage of between about 5 percent and about 12 percent coenzyme Q-10 or analog thereof, based on the total amount of said coenzyme Q-10 or analog thereof administered.

2. The composition of claim 1, wherein said coenzyme Q-10 or an analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.

3. The composition of claim 1, wherein said monoterpene is limonene or a derivative thereof.

4. The composition of claim 3, wherein said limonene derivatives are selected from the group consisting of perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

5. The composition of claim 1, wherein said composition is in the form of a solution, an elixir, a suspension, or a capsule.

6. The composition of claim 5, wherein said capsule is a soft gelatin capsule.

7. The composition of claim 6, wherein said carrier is soybean oil.

8. A solubilized coenzyme Q-10 composition comprising:

coenzyme Q-10 or an analog thereof;

a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof; and

an acceptable carrier, wherein said composition provides a steady state plasma level concentration of between about 2.5 μg/ml to about 3.5 μg/ml of coenzyme Q-10 or analog thereof.

9. The composition of claim 8, wherein said coenzyme Q-10 or an analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.

10. The composition of claim 8, wherein said monoterpene is limonene or a derivative thereof.

11. The composition of claim 10, wherein said limonene derivatives are selected from the group consisting of perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

12. The composition of claim 8, wherein said composition is in the form of a solution, an elixir, a suspension, or a capsule.

13. The composition of claim 12, wherein said capsule is a soft gelatin capsule.

14. The composition of claim 13, wherein said carrier is soybean oil.

15. A solubilized coenzyme Q-10 composition comprising:

coenzyme Q-10 or an analog thereof;

a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof; and

an acceptable carrier, wherein said composition provides a peak plasma level of between about 2.1 μg/ml to about 3.0 μg/ml of coenzyme Q-10 or analog thereof.

16. The composition of claim 15, wherein said coenzyme Q-10 or an analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.

17. The composition of claim 15, wherein said monoterpene is limonene or a derivative thereof.

18. The composition of claim 17, wherein said limonene derivatives are selected from the group consisting of perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

19. The composition of claim 15, wherein said composition is in the form of a solution, an elixir, a suspension, or a capsule.

20. The composition of claim 19, wherein said capsule is a soft gelatin capsule.

21. The composition of claim 20, wherein said carrier is soybean oil.

22. A method for the delivery of coenzyme Q-10 or analog thereof that provides an absorbed percentage of coenzyme Q-10 or analog thereof of between about 5 percent and about 12 percent of said coenzyme Q-10 or analog thereof, to an individual in need thereof, comprising the steps of

providing a composition that comprises coenzyme Q-10 or analog thereof solubilized in a monoterpene and an acceptable carrier, such that the individual's blood level has absorbed between about 5 percent and 12 percent of the total amount of coenzyme Q-10 or analog thereof provided to the individual.

23. A method for the delivery of a steady state plasma level of between about 2.5 μg/ml to about 3.5 μg/ml coenzyme Q-10 or an analog thereof, to an individual in need thereof, comprising the steps of

providing a composition that comprises coenzyme Q-10 or analog thereof solubilized in a monoterpene and an acceptable carrier, such that the individual's blood level contains between about 2.5 μg/ml to about 3.5 μg/ml of coenzyme Q-10 or analog thereof at steady state.

24. A method for the delivery of a peak plasma level of between about 2.1 μg/ml to about 3.0 μg/ml coenzyme Q-10 or analog thereof, to an individual in need thereof, comprising the steps of

providing a composition that comprises coenzyme Q-10 or analog thereof solubilized in a monoterpene and an acceptable carrier, such that the individual's blood level contains between about 2.1 μg/ml to about 3.0 μg/ml of coenzyme Q-10 or analog thereof at peak plasma level.

25. A packaged nutraceutical formulation comprising:

coenzyme Q-10 or an analog thereof, and a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, wherein said formulation is encapsulated in a gelatin capsule; and

instructions for use thereof, such that an individual's blood level has absorbed between about 5 percent and 12 percent of the total amount of coenzyme Q-10 or analog thereof provided to the individual.

26. A packaged nutraceutical formulation comprising:

coenzyme Q-10 or an analog thereof, and a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, wherein said formulation is encapsulated in a gelatin capsule; and

instructions for use thereof, such that an individual's blood level contains between about 2.5 μg/ml to about 3.5 μg/ml coenzyme of Q-10 or analog thereof at steady state.

27. A packaged nutraceutical formulation comprising:

coenzyme Q-10 or an analog thereof, and a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 or analog thereof, wherein said formulation is encapsulated in a gelatin capsule; and

instructions for use thereof, such that the individual's blood level contains between about 2.1 μg/ml to about 3.0 μg/ml coenzyme of Q-10 or analog thereof at peak plasma level.

FIGURE 1

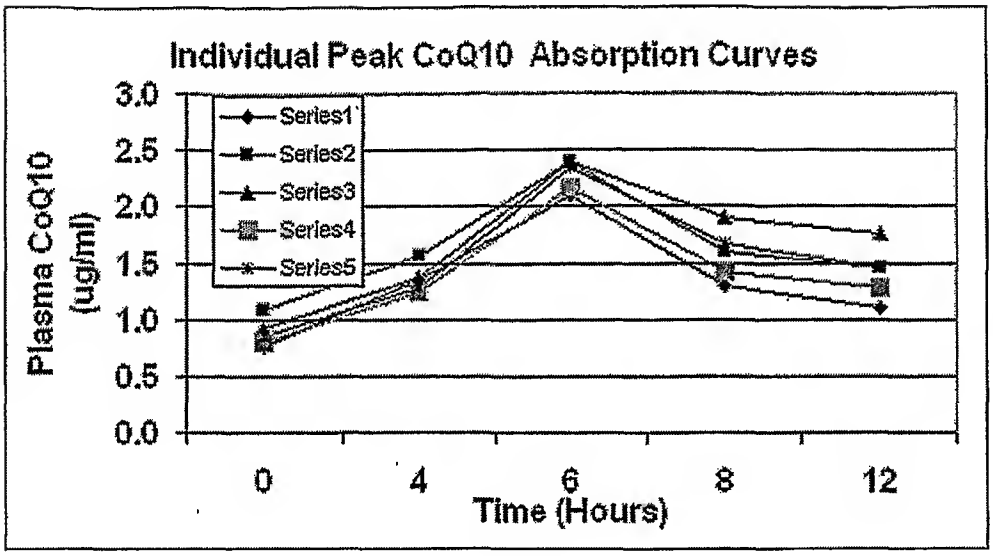


FIGURE 2

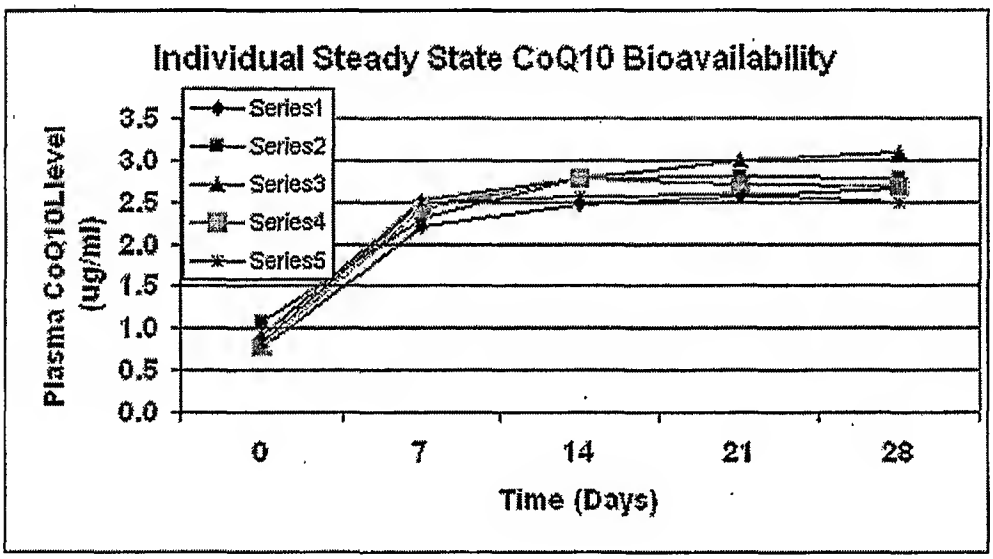


FIGURE 3

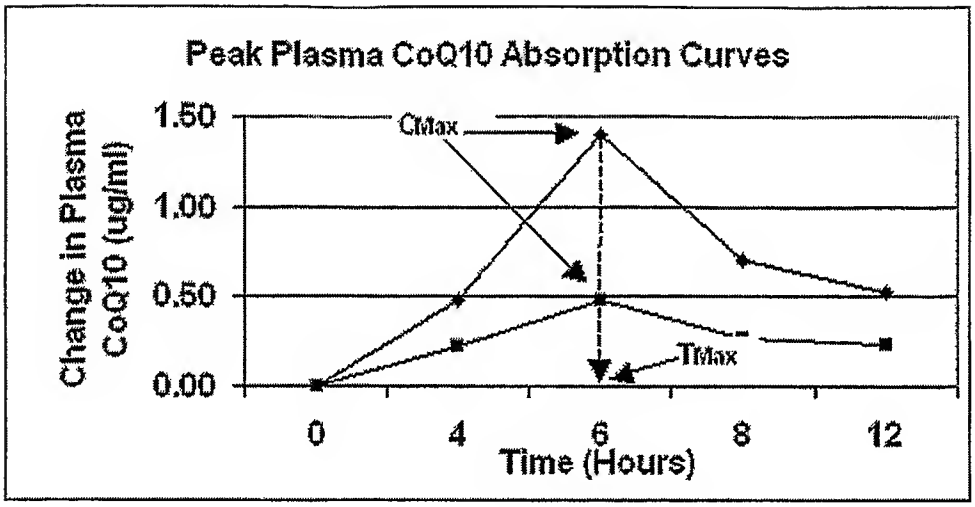
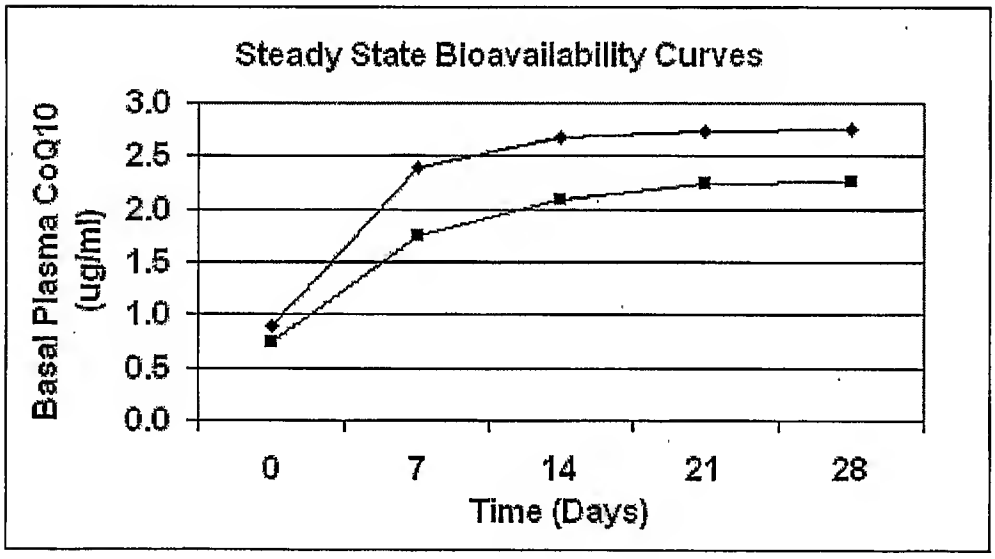


FIGURE 4



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/122

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 198216 Derwent Publications Ltd., London, GB; Class A96, AN 1982-31657E XP002313489 -& JP 57 042616 A (FREUND SANGYO KK) 10 March 1982 (1982-03-10) abstract	1-27
X	US 2003/147927 A1 (NAZZAL SAMI ET AL) 7 August 2003 (2003-08-07) claims	1-6, 8-13, 15-20, 22-27

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2005	02/02/2005

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